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The current and future burden of late-onset dementia in the United Kingdom: Estimates and interventions

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Abstract: INTRODUCTION: We estimate the burden of late-onset dementia in the United Kingdom through to 2025 and assess the impact of potential interventions. **METHODS:** We compute disability adjusted life years (DALYs) through to 2025 and consider three interventions, all assumed launched in 2018; (1) an optimistic limiting case of a 100% preventive intervention with immediate uptake of 100% of the population at risk; (2) an intervention which delays onset by 5 years, linear uptake to 50% after 5 years; (3) as (2) but uptake 75% after 5 years. **RESULTS:** By 2025, the DALY burden will have increased by 42% from the Global Disease Burden 2010 estimate. Intervention results: (1) a 9% decrease by 2025; (2) a 33% increase; and (3) a 28% increase. **DISCUSSION:** At current prevalence rates, the ability of an intervention to offset the projected increase in DALY burden of dementia in the United Kingdom by 2025 appears low.

DOI: <https://doi.org/10.1016/j.jalz.2016.03.013>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-124053>

Journal Article

Accepted Version

Originally published at:

Lewis, Fraser I; Torgerson, Paul R (2017). The current and future burden of late-onset dementia in the United Kingdom: Estimates and interventions. *Alzheimer's Dementia*, 13(1):38-44.

DOI: <https://doi.org/10.1016/j.jalz.2016.03.013>

The current and future burden of late-onset dementia in the UK: estimates and interventions

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Abstract

Background: We estimate the burden of late-onset dementia in the United Kingdom through to 2025 and assess the impact of potential interventions.

Methods: We compute disability adjusted life years (DALYs) through to 2025 and consider three interventions, all assumed launched in 2018; i) an optimistic limiting case of a 100% preventive intervention with immediate uptake of 100% of the population at risk; ii) an intervention which delays onset by five years, linear uptake to 50% after five years; iii) as ii) but uptake 75% after five years.

Results: By 2025 the DALY burden will have increased by 42% from the Global Disease Burden (GDB) 2010 estimate. Intervention results: i) a 9% decrease by 2025; ii) a 33% increase; and iii) a 28% increase.

Conclusions: At current prevalence rates, the ability of an intervention to offset the projected increase in DALY burden of dementia in the UK by 2025 appears low.

1. Introduction

The risk of developing dementia increases markedly with age, and with the global population – both developed and developing countries - ageing rapidly [1] dementia has the potential to be a major future health concern. It has been estimated that by 2050 the number of people living with dementia could be 131.5 million compared to 46 million currently [2]. Considerable scepticism is clearly needed with such long extrapolations, in particular with some recent analyses suggesting a potential stabilisation in (age-specific) prevalence and possibly even a decrease [3]. However, the latter also requires caution as out of five studies examined by Wu et al. [3] only one demonstrated a statistically significant reduction.

Our focus in the present study is to estimate the future burden of dementia in the UK over the relative short term – from 2015 through 2025 - and more importantly, to quantify to degree to which this burden might be reduced through possible interventions. A number of earlier studies have developed future projections of the prevalence of dementia and are reviewed in [4]. There are very few studies which assess the future impact of hypothetical interventions. Vickland [5] presented a simulation model aimed at virtual experimentation with respect to prevalence and dynamics of dementia, and provided their model as an online tool (web link no longer active). Several modelling studies have also been commissioned by dementia advocacy organizations, such as the Alzheimer's Association [6] and Alzheimer's Research UK [7].

In this study we assume that prevalence is fixed at recent estimates and measure burden in disability adjusted life years (DALYs), comparing our estimates with those in the Global Disease Burden (GDB) 2010 [8] (with UK specific estimates for 1990 and 2010 in [9]). To our knowledge, the modelling methodology we utilize here (partial differential equations) has not before been applied in dementia, despite being a standard technique in epidemiology for dealing with ageing (p.621 in [10]). A major advantage of

this methodology is its transparency - such models are not “black boxes” but are defined by an explicit set of equations allowing our analyses and results to be readily scrutinized, replicated and adapted/extended by other researchers.

Alzheimer’s disease (AD), which accounts for over 60% of all cases of dementia in the UK [11], has among the lowest number of compounds successfully progressing to regulatory review of any therapeutic area [12]. In 2015 press reports ([13], [14], [15], [16]) suggested that new molecules currently in development might have the ability to slow impairment or progression of AD or mild cognitive impairment, with several of these products about to enter phase III trials. If some of these molecules receive marketing authorisation, it will likely be some years before they reach patients. Current estimates [17] suggest it can take on average 2.5 years for a phase III trial and then 1.5 years from application for marketing authorisation to launch. Once launched, patient access to a medicine can be far from immediate. In the UK, for example, it currently takes approximately five years from the launch of a new medicine to reach most of the patient population ([18], chart 17).

Here we consider the impact of interventions introduced in three years' time [from this writing] (2018) that have phased uptake. Three years is shorter than reported average times in the literature because of a number of initiatives underway in both the United States and Europe aimed at fast tracking high priority medicines for market authorisation approval. While we have currently framed intervention in the context of a new medicine, our scenarios are generic in that they examine the impact of different degrees of delay in onset on future burden, and such a delay in onset could also be attributable to risk reduction measures or cohort effects as discussed in [3].

2. Methods

We use an incidence based approach to estimate DALYs and assumptions consistent with [8]. Specifically, no discounting of future health and no age-weights are used. Our estimates for 2025 are compared with those from the GDB 1990 and GDB 2010. We indirectly estimate incidence and mortality from available data via a mathematical model. The duration of dementia is sourced directly from the literature [19]. We use an identical methodology to compute DALYs for males and females, but these analyses are undertaken independently. We defer most technical details to the online supplementary material (see S1-S6). All modelling was conducted in Mathematica 10.0 and Mathematica notebooks are provided to enable our results to be reproduced (see the supplementary information for more details).

2.1 Model definition

We utilize an epidemiological model which is jointly continuous in both age and time. The rationale for this is simple: i) dementia is an age driven disease; and ii) we wish to assess its impact on the population through time, as driven by demography. Our model is a standard formulation (e.g. [20] [21]) and follows the familiar susceptible-infected (SI) compartmental model structure [22], but extended to include both age and time. A more appropriate nomenclature here is susceptible-diseased (SD). A difference from models commonly used in burden analyses, e.g. in DISMOD-type software [23], is that rather than a model that is defined by a system of ordinary differential equations (ODEs), our model is defined by a system of partial differential equations (PDEs).

Our model is:

$$\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} = -\mu_1(a, t)S - \lambda(a, t)S; \quad (1)$$

$$\frac{\partial D}{\partial a} + \frac{\partial D}{\partial t} = -\mu_2(a, t)D + \lambda(a, t)S - \delta(a, t)D;$$

and (2)

where $S = S(a, t)$ is the number of people of age a and at time t who do not have

dementia (for susceptible) and $D = D(a, t)$ is the number of people of age a and at

time t who do have dementia (for diseased). Equation 1 states that we have a flow out of the susceptible class of individuals due either to death (but not death due to

dementia) at rate $\mu_1(a, t)$ per capita per unit time, or else due to developing dementia at

rate $\lambda(a, t)$ per capita per unit time. In the dementia class (equation 2) there is a higher flow out of the population than in the susceptible class as individuals may now die due to dementia in addition to other causes. The total per capita per unit time death rate in the

dementia class is $\mu_2(a, t) + \delta(a, t)$, the latter term being the dementia-specific death rate,

the former term is the death rate for dementia suffers but where the main cause of

death is not dementia, and we assume $\mu_2(a, t) \geq \mu_1(a, t)$. This is to allow people with dementia to have at least the same average death rate as the rest of the population, i.e. those without dementia, and possibly greater (but not less, all else being equal), as dementia may be a contributory factor to deaths where the primary cause recorded on

the death certificate is not dementia. A number of studies have suggested that deaths due to dementia may be considerably under-reported in official death registrations [24].

While compact, the model defined in equations 1 and 2 is deceptively flexible as it allows all flows in the population to vary continuously with age, and also if necessary with time. The former is clearly biologically important for both dementia and mortality in people

aged 60 and over. Given appropriate estimates for $\mu_1(a, t)$, $\mu_2(a, t)$, $\delta(a, t)$ and $\lambda(a, t)$,

equations 1 and 2 can be solved to give values for S and D for any desired age (60 and above) and for any desired year (2013 onwards). To calculate annual DALYs we first

compute annual years of life lost (YLL) by evaluating

$$\iint_{t=y_1, a=60}^{t=y_2, a=\infty} \delta(a, t) D(a, t) L(a) da dt$$

where $L(a)$ is the duration of lifetime remaining at age a . This expression is the total flow out of the dementia class due to deaths due to dementia in time period y_1 through to y_2 weighted by remaining life expectancy. The years living with disability (YLD) component

is estimated by evaluating

$$\iint_{t=y_1, a=60}^{t=y_2, a=\infty} \lambda(a, t) S(a, t) \rho(a) W da dt$$

where $\rho(a)$ is the duration of

survival of dementia for onset at age a , and w is the disability weight for dementia (this is an average across severity stages – see data sources section later for more details). This expression is the total flow into the dementia class in time period $y1$ through to $y2$ weighted by duration and disability weight.

2.2 Data sources

We require five types of data: i) prevalence; ii) mortality; iii) population projections; iv) dementia survival duration; and v) disability weights. Details are provided below. Note that the data sources used in ii) through iv) all relate to England and Wales only. Our modelling focuses on England and Wales as it has the most comprehensive data and accounts for the vast majority of the UK (89% of the UK population based on latest Office for National Statistics (ONS) mid-year 2014 population estimates). In our results we report UK level DALY estimates using a simple pro-rata adjustment, i.e. multiplication by $1/0.89$.

2.2.1 Prevalence estimates

Estimates of dementia prevalence in the UK were published in 2014 by the Alzheimer's society [11]. These are expert opinion based Delphi consensus estimates, assumed to be correct circa 2013, and a common methodology in dementia studies, e.g. [25].

Estimates are available separately for males and females and in five year age bands from 60 through to 90 years, the upper-most age band is 95+. Empirical estimates are available from the CFAS I (1989-94) and CFAS II (2008-11) studies [26]. We utilize the current Alzheimer's society prevalence estimates as while – all else being equal – it might be preferable to use empirical rather than expert opinion based estimates, the former are more recent and also avoid relying on a single geographically limited study.

2.2.2 Mortality data

We use death registrations in calendar year 2013 for England and Wales, which are provided by the ONS. These are counts broken down by sex, main cause of death using ICD10 codes (dementia is F01/F03), and in five year age bands up to 95+. We use both the numbers of total deaths for 2013 and deaths whose main cause was dementia.

2.2.3 Population projections

We use 2012-based population principal projections provided by the ONS which provides estimates of the total population size in England and Wales, broken down by sex, for individual years 2012 through 2025, and individual year of age in the interval 0 through 89, then age bands 90-94, 95-99 and 100+. Principal projections are the ONS' primary estimates.

2.2.4 Duration of dementia

We use estimates from Table 2 in [19] which come from a prospective study in England and Wales which followed a cohort of 438 patients for 14 years (1991-2003). This provided estimates of survival time in years by sex and median age at onset, where the latter was grouped into age bands 65-69, 70-79, 80-89, 90+. Estimates of survival time vary in the literature and we use [19] as this captures onset and diagnosis within a short period of time, and is also from a UK cohort.

2.2.5 Disability weights

We use the disability weights for dementia from the GDB 2010 [27]. This gives three separate weights, one for each stage: mild; moderate; severe. We do not model stages of severity (see Discussion), and use a single disability weight which is the average value across the three point estimates for mild, moderate and severe (see Table 2 in [27]) .

2.3 Baseline Scenario – Projection due to Ageing Population

Our baseline scenario estimates future DALYs without any intervention and we assume (age-sex specific) prevalence in the future is fixed at current estimates. It is unclear how reasonable or otherwise such an assumption is, but in the absence of better data we consider this appropriate for the current study. The model fitting process is conceptually straightforward (see S2 for technical details). We use numerical optimization techniques

to calibrate our model so that the state variables, $S(a, t)$ and $D(a, t)$, are a close match to their “empirical equivalents”. By empirical equivalents we mean the projected age-sex distribution of the number of people with and without dementia across ages 60 upwards and years 2013 through 2025. These distributions are straightforward to calculate as all that is required is multiplying the age-sex specific prevalence estimates from the Alzheimer’s society by the age-sex specific population projections from the ONS. The rationale here is that if our model is able to produce output which approximates these empirical estimates, then that provides us with confidence that the model parameters will be epidemiologically reasonable and therefore suitable for estimating disease burden and impacts of interventions.

2.4 Intervention scenarios

We consider three intervention scenarios. Firstly, we assume – unrealistically, but which serves as a limiting best case – that a person on this intervention at age 60 or older will not develop dementia. We assume that this intervention will be introduced at 2018 and have immediate and 100% uptake. To estimate the impact of this scenario we run our

model with $\lambda(a, t)$, the age-dependent per capita incidence rate, adjusted so that between

2013 and 2018 this is as estimated for the baseline scenario, but from 2018 we set

$$\lambda(a, t) = 0$$

for all $t > 2018$ and for all ages a . In other words there are no new cases of

late-onset dementia in the population from year 2018 onwards.

For the second and third scenarios we consider a more realistic situation where it is assumed that the intervention delays the rate at which an individual develops dementia by five years compared with the baseline. For example, this intervention reduces the rate at which a male aged 80 develops dementia to that of a male aged 75. This form of delay explicitly acknowledges the key role of ageing. We assume that only 50% (scenario two) or 75% (scenario three) of the population at risk from dementia have access to the intervention. We also assume a (linear) phased uptake, so for scenario two we have 10% uptake in 2018, 20% in 2019 increasing up to 50% in 2022. To implement

this scenario we adjust $\lambda(a, t)$ so that when $2019 \geq t > 2018$ we have

$$\lambda^*(a, t) = 0.9 \lambda(a, t) + 0.1 \lambda(a - 5, t)$$

, for $2020 \geq t > 2019$ we have

$$\lambda^*(a, t) = 0.8 \lambda(a, t) + 0.2 \lambda(a - 5, t)$$

and similarly for the other three years. Scenario three is

implemented the same way but where the annual uptake increments are in steps of 15% rather than 10%.

In S5 we briefly consider an additional intervention which is assumed to provide a guaranteed period of protection, e.g. five years, independently of age. This is considerably more extreme than scenarios two and three examined here, but may be

more similar to what was assumed in [6] (although this is unclear due to the lack of details provided in [6]).

3. Results

See S1-S4 for model validation details and figures showing a comparison of the fit of our model to the empirical data. S5 contains additional results, and S6 details of how to replicate all results presented using the Mathematica notebooks (and equivalent PDFs) provided.

3.1 Baseline Scenario – Projection due to Ageing Population

For 2015 we estimate a burden of approximately 440K (i.e. 440,000) DALYs. As a common sense check against the GDB for the UK [9], in 1990 this was estimated as between 163K and 313K DALYs (mean 220K), rising to between 304K and 488K DALYs by 2010 (mean 387K). This is a simple (i.e. not compounded) annual percentage growth rate of 3.8%. If we trend forward at the same rate from 2010 by another 5 years we get between 362K and 581K DALYs (mean 461K). Our estimate is within these - admittedly rather wide - confidence bounds.

Figure 1 shows a comparison of historical estimates from the GDB 1990 and GDB 2010 with our forward projections. For 2020 and 2025 we estimate 494K and 551K DALYs. From the GDB estimate for 2010 through to our estimate for 2025 gives a relative increase in DALYs of 42%.

3.2 Intervention impacts

For our first intervention, 100% uptake of a complete preventive therapy, there is a consistent decrease in DALYs from the introduction of the intervention (Figure 1), dropping to 416K DALYs by 2020 and to 353K DALYs by 2025, these are decreases of 16% and 36% respectively from the baseline case at 2020 and 2025. From the GDB estimate for 2010 through to our estimate for 2025 gives a relative decrease in DALYs of 9%.

The second intervention, a five year delay in the onset of dementia with a staged uptake of 50% after five years, gives a DALY burden of 489K at 2020 and 515K at 2025. Compared to baseline, this intervention gives decreases of 1% and 7% respectively for 2020 and 2025. From the GDB estimate for 2010 through to our estimate for 2025 under this intervention gives a relative increase in DALYs of 33%.

The third intervention is similar to the second intervention but with a higher uptake rate of 75% after five years. This intervention gives a DALY burden of 486K at 2020 and 497K at 2025, compared to baseline these are decreases of 1% and 10% respectively. From the GDB estimate for 2010 through to our estimate for 2025 under this intervention gives a relative increase in DALYs of 28%.

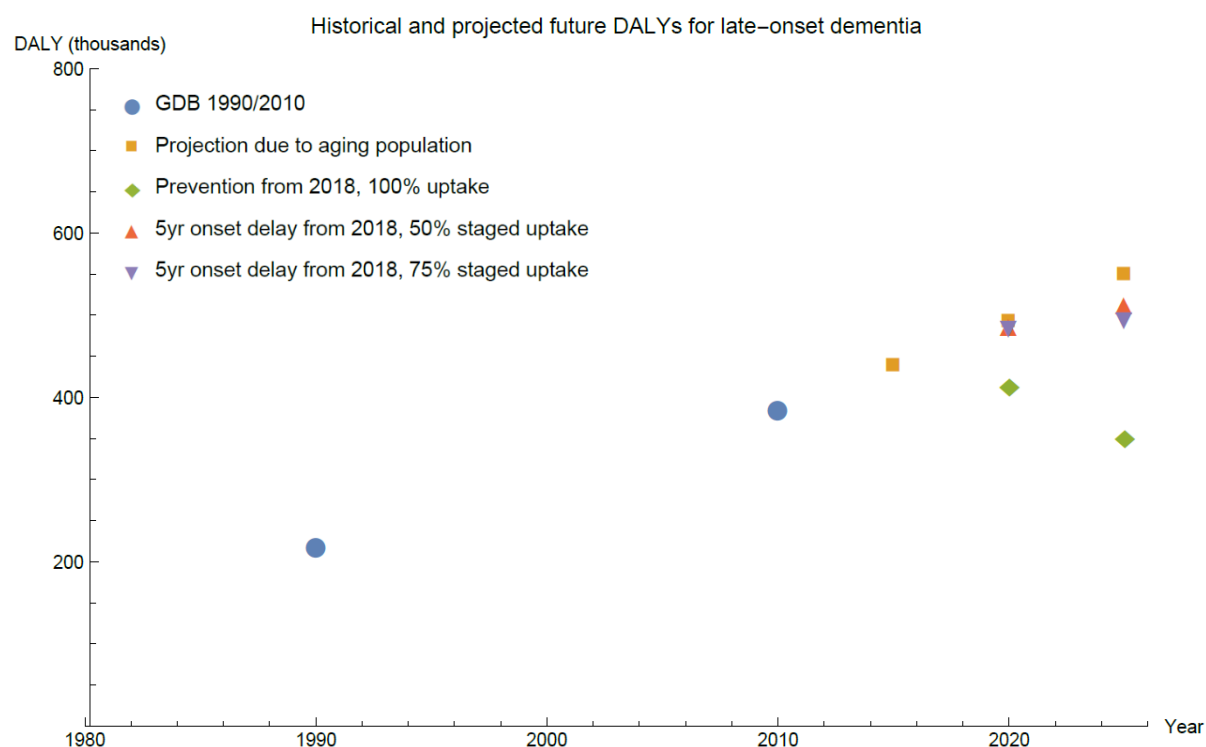


Figure 1. Historical and projected future DALYs for late-onset dementia in the UK

4. Discussion

Our results suggest that only the unrealistic scenario of a 100% preventive therapy with instantaneous 100% uptake in 2018, would offset the increasing DALY burden of late-onset dementia in the UK due to population ageing. The other two intervention scenarios, while more realistic do still make some optimistic assumptions, and even in this context result in only minor decreases in the projected DALY burden by 2025; increases of 33% and 28% from the GDB 2010 estimate, compared to an increase of 42% without any intervention.

Our results have a simple message from a policy perspective; the burden of dementia in the UK is likely to increase considerably by 2025, and on this time-scale the practical impact of therapeutic interventions still under development will have little, if any, impact, against the force of an ageing population. This means that demand for health and social care for dementia sufferers is likely to increase considerably over the next 10 years,

irrespective of the increasing amount of funds put into global dementia funding, such as the \$100m Dementia Discovery Fund. Current topical issues, such as the potential existence of a cohort effect in reducing prevalence between now and 2025, would need to be very substantial to offset the impact of population ageing.

4.1 Study limitations

4.1.1 Point estimates

As with all modelling studies we have made a number of simplifying assumptions. Firstly our modelling is concerned only with point estimates and we make no attempt to attach corresponding estimates of uncertainty. The three main data sources for our modelling are the ONS population projections for England and Wales, ONS deaths registrations and the Alzheimer's Society prevalence estimates. The first does not come with any estimates of uncertainty (e.g. prediction error), the second is a population level (i.e. census) value and therefore has no uncertainty. The Delphi consensus estimates of prevalence do not come with uncertainty estimates. The parameters in our model are estimated from these data and combined with the fact that our model is itself deterministic, then limiting our analyses to point estimation seems entirely appropriate.

4.1.2 Future prevalence

We have applied current prevalence estimates to the future UK population, as mentioned above it is unclear how reasonable or otherwise such an assumption is. In the absence of better data – in particular concerning robust quantification of any potential cohort effects on future dementia incidence - we consider this appropriate for the current study.

4.1.3 Severity states

We have not attempted to model progression of severity. This would be a worthy area of future work if sufficient data were to become available to enable estimation of the duration of the mild/moderate/severe stages for different ages of onset (and also by sex

if appropriate). In particular, this would allow consideration of interventions which delay progression as opposed to delaying onset.

4.2 Comparison with existing intervention results

While our analyses are not directly comparable with those from the Alzheimer's Association [6] (as different outcome variables are used, different time horizons, and no methodological details are given), some general remarks may be useful as [6] report somewhat more optimistic results. One potentially major (assumed) difference is in methodology. We use a dynamic model, i.e. an incidence-based approach, which is also continuous in age and time. This enables our model to – as much as is reasonably practicable – mimic reality, i.e. continuous age progression and acquisition of dementia in the UK population. An alternative is to use a static (e.g. prevalence-based) model. The latter are typically much simpler to construct and parameterize, but the price for this is that they are much further removed from the real system about which we are attempting to learn – which here is fundamentally dynamic in nature. In the incidence-based approach, all health outcomes, including those in future years, are assigned to the initial event. This approach therefore reflects the future burden of disease resulting from current events (i.e. onset of dementia). In the prevalence-based approach, the health status of a population is assessed at a specific point in time, and prevalent diseases are attributed to initial events that happened in the past [28]. Consequently, prevalence based approaches to disease burden estimates underestimate the burden for chronic diseases where the population size is increasing. Dementia is such a chronic disease that is affecting an increasing population of old people.

A second potential explanation for differences in results between our modelling and that in [6] is how the intervention was actually defined and implemented, e.g. using a guaranteed period of protection independent of age would be expected give more

optimistic results. For our third intervention we estimate an increase of 26% in the burden of disease from the GDB estimate for 2010 through to 2022, whereas using a guaranteed protection of five years, as (assumed) used by the Alzheimer's Association, and similar staged uptake, the projected increase in burden is 17%. See S5 for additional details of this comparison.

4.3. Summary

The results of our analyses can be distilled down into two key findings: firstly, that it is essential to plan for increasing numbers of dementia patients requiring care in the UK over the next ten years; and secondly, that there is a clear need for more detailed descriptive studies in order to better elucidate key epidemiological parameters, and therefore improve the accuracy and level of detail which can be explored when assessing the impact of potential interventions.

Acknowledgements

We thank Prof. Martin Knapp for useful discussions on modelling dementia incidence. The views expressed by the authors in this paper are not those of the OHE or the ABPI. The Office of Health Economics is supported by an annual grant from the Association of the British Pharmaceutical Industry.

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